Notice of Opportunity for Collaboration

MULTI-CENTER CLINICAL TRIALS OF NOVEL THERAPIES AND DIAGNOSTICS FOR PATIENTS WITH CHRONIC HEPATITIS B

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) seeks collaborations with industry to provide novel therapeutic agents, diagnostic markers and devices for studies of patients with well-characterized chronic hepatitis B.

INTRODUCTION: Chronic hepatitis B is due a persistent infection with hepatitis B virus (HBV) and is a major cause of cirrhosis, end-stage liver disease and hepatocellular carcinoma. Chronic infection with HBV affects an estimated 1.5 million Americans and it is the underlying reason for approximately 10 percent of liver transplants done in the United States. There are currently six different agents licensed and approved for use as therapeutic agents in patients with chronic hepatitis B. However, there remain many questions regarding the use of these agents such as: Which patients with chronic hepatitis B should be treated? Which agent or agents are most efficacious? Should agents be used alone or in combination with other therapies? For how long should the agents be used? What viral, biochemical or clinical markers should be used to monitor success or failure of therapy? Currently available therapies are effective for the treatment of patients with advanced disease due to hepatitis B, however it is not clear whether these therapies effect the long-term natural history of mild and moderate forms of chronic HBV infection. A large proportion of patients with chronic HBV infection have no symptoms or signs of liver disease and have minimal disease activity as assessed by biochemical and histological features; it is not clear whether these patients would benefit from treatment. At present, the criteria for treatment of hepatitis B are controversial.

In response to the challenges surrounding management of chronic hepatitis B, the NIDDK has proposed creation of a Hepatitis B Clinical Research Network (Hepatitis B Network) to create a large database of patients with chronic HBV infection and allow for clinical investigation into the pathogenesis of liver injury, the natural history of infection and long-term antiviral therapy in different categories of patients. This study would include patients with the full spectrum of clinical severity of disease, from patients with the inactive hepatitis B surface antigen (HBsAg) carrier state, to patients with mild but active HBV infection ("immune tolerant"), to patients with typical hepatitis B e antigen (HBeAg) positive chronic hepatitis B as well as negative chronic hepatitis B (HBeAg), and patients with cirrhosis. The Hepatitis B Network will be charged with conducting investigational, natural history as well as therapeutic studies and ancillary studies of etiology and pathogenesis.

The proposed Hepatitis B Network will include up to 10 Clinical Centers in North America which will be charged with enrolling at least 1,000 patients over a 7 year period. A central data coordinating center will maintain the database and be responsible for the quality and accuracy of the data and adherence to regulatory requirements. The Hepatitis B Network will include a virology and immunology center which will be charged with testing serum and tissue samples for HBV DNA and assessing the replicative status of HBV in the liver and immune reactivity to HBV antigens in the peripheral blood and intra-hepatic lymphocytes of enrolled patients. In addition to collecting clinical patient data, the Hepatitis B Network will submit liver biopsy, serum, DNA and other samples to a central repository. These resources will allow for many ancillary studies on the natural history, pathophysiology, and diagnosis of hepatitis B and will provide multiple opportunities for collaboration with industry in areas such as genetic factors, proteomics, metabolomics, imaging, and biomarkers for disease activity and hepatic fibrosis, the determinants of progression and severity of chronic hepatitis B. The Hepatitis B Network will also be charged with developing prospective controlled trials to evaluate important issues in treatment, such as (but not limited to) the role of combination versus monotherapy using nucleoside analogues and the role of peginterferon in the management of HBeAg-positive and -negative chronic hepatitis B.

STUDY GOALS: In preparing to establish a Hepatitis B Clinical Research Network, the NIDDK wishes to consider the potential application of diagnostics and therapeutics for patients with chronic hepatitis B. The overall goal of the Hepatitis B Network will be to perform clinical, epidemiological and therapeutic research in patients with chronic hepatitis B using a standardized and coordinated approach to the evaluation and therapy of chronic hepatitis B and to provide sufficient numbers of patients for the research. This will be done by development of a database on chronic hepatitis B patients including clinical information as well as liver, serum and DNA samples.

SUMMARY: The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) is seeking proposals in the form of capability statements from companies that are interested in collaborating with a proposed Hepatitis B Clinical Research Network by providing novel therapeutic agents, diagnostic markers or devices for investigational studies as well as randomized, placebo-controlled, multicenter clinical trials of approaches to therapy, which could include: (1) assays for HBV DNA levels as well as determination of nucleotide sequence or special tests for genotyping, identification of viral mutants; (2) assays for hepatitis B markers including levels of HBsAg, HBeAg, and antibodies to hepatitis B; (3) non-invasive markers or imaging tests that might reflect state of viral replication, disease activity and degree of hepatic fibrosis that is currently only assessable by liver biopsy; (4) biomarkers for early detection of hepatocellular carcinoma in these high risk patients, using approaches such as proteomics, serum tumor markers and imaging tests, (5) antiviral agents for hepatitis B including nucleoside analogues, combinations of nucleoside analogues and peginterferon; (6) novel antiviral agents that might have yet to be proven effective in chronic hepatitis B and might be used in pilot clinical trials such as small molecule inhibitors of other steps in the HBV replicative cycle, molecular therapies aimed at HBV DNA such as siRNAs, and immunological therapies such as therapeutic vaccines or cytokines/anticytokines; (7) novel hepatoprotective therapies that might ameliorate the disease or enlist natural antiviral activity such as anti-oxidants, immune stimulants and cytokines; and (8) complementary therapies such as herbal medicines.

SUPPLEMENTARY INFORMATION: Collaborative arrangements may be either Clinical Trial Agreements or Cooperative Research and Developments Agreements (CRADAs) pursuant to the Federal Technology Transfer Act of 1986 (FTTA, 15 U.S.C. 3710; and Executive Order 12591 of April 10, 1987, as amended by the National Technology Transfer and Advancement Act of 1995), as appropriate. Clinical Trial Agreements and CRADAs are agreements designed to enable certain collaborations between Government laboratories and non-Government laboratories. They are not grants, and not contracts for the procurement of goods/services. The NIDDK is prohibited from transferring funds to a Clinical Trial or CRADA collaborator. Under a CRADA, NIDDK can contribute facilities, staff, materials, and expertise to the effort. The collaborator typically contributes facilities, staff, materials, expertise, and funding to the collaboration. The CRADA collaborator receives an exclusive option to negotiate an exclusive or non-exclusive license to Government intellectual property rights arising under the CRADA in a pre-determined field of use and make contributions that qualify one or more of its employees as a co-inventor(s) of new technology developed under the CRADA. Examples of the Clinical Trial Agreement and the CRADA can be found at http://techdev.niddk.nih.gov/.

CAPABILITY STATEMENTS: The NIDDK will utilize the information provided in the Collaborator Capability Statements received in response to this announcement to help in development of a Hepatitis B Clinical Research Network. It is the intention of the NIDDK that all qualified Collaborators have the opportunity to provide information through their capability statements. The Capability Statement should not exceed 10 pages of narrative and should address the following selection criteria:

1. The proposed preparation must have been tested in Phase I trials in humans.
2. The statement should provide specific details of the methods to be utilized in the investigation of therapeutic agents including drugs, biologics, and devices in patients with chronic hepatitis B and clearly describe important issues surrounding the evaluation of disease management in these patients.
3. The statement should include a detailed plan demonstrating the ability to provide sufficient quantities of the laboratory test agents in a timely manner for the duration of the study.
4. A description of laboratory tests that are needed including assays and required amount of specimens, to determine specific biomarker levels along with appropriate methods for performing.
5. A description of other core facilities and interactions with core facilities that are needed.
6. A description of the methods that would be used to assure privacy and maintain confidentiality of data.
7. The statement may include outcome measures of interest to the Collaborator. The specifics of the proposed outcome measures and the proposed support should include but not be limited to treatment and evaluation of chronic hepatitis B, personnel, services, facilities, equipment, or other resources that would contribute to the conduct of the commercial development.
8. If appropriate, specific funding commitment to support the advancement of scientific research.
9. Must agree to have their preparation used in the above-mentioned Hepatitis B Network-developed protocols which will be conducted by the Network and will have data collection and analysis performed by the Hepatitis B Network's Data Coordinating Center.
10. Must provide IND sponsor of the studies with cross-reference access to a US FDA filing that contains the chemistry, manufacturing and controls information for the drug substance and drug product.
11. Dosing and Pharmacokinetic data from human studies must be provided for novel agents**.**
11**.** Adverse event profile from human studies must be provided.
12. Must agree to share (with NIDDK and potentially the Hepatitis B Network) all safety data from other studies involving their preparation as well as relevant efficacy data from other studies (updated Investigator Brochure, etc).
13. The statement must address willingness to promptly publish research results.

SUBMISSION DATES: Only written capability statements received by the NIDDK on or before February 1, 2007 will be considered. Applicants meeting the criteria as set forth in this announcement will be invited at the Applicants own expense to discuss with the Hepatitis B Network Steering Committee their plans, capabilities, and research findings pertinent to the study at a meeting of the Hepatitis B Network Steering Committee in the future.

CONTACT INFORMATION: Submit Capability Statements to:
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A formatted version of the Notice of Opportunity will be posted at:
http://techdev.niddk.nih.gov/collabs.htm.